THE GENETICS OF THE BLOOD-GROUPS

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Up to the present time nine different systems of blood groups have been discovered. This does not include a few others which are so rare that they have been found in a single family group only and so are of little importance. The story is becoming extensive, but as regards inheritance it remains remarkably simple. In fact, there is no more simple and straightforward subject in the whole of genetics, and in order to understand it only a few elementary concepts in genetics and serology are required.

The blood groups are determined by chemical substances, antigens, situated on the surface of the erythrocytes. The presence of an antigen is disclosed when an antiserum becomes available containing antibodies which will react with the red cells bearing that antigen. It was no accident that the ABO system should have been the first to be discovered; this was in 1900. The reason is that the antibodies occur naturally; in fact, almost all persons who lack antigen A on their red cells have anti-A in their serum, and similarly for B. Hence, of course, the prime importance of the ABO groups in transfusion. No other antibodies occur naturally, or at least only as very occasional rare exceptions or in very weak form. It was not until 1927 that the second and third systems, MN and P, were discovered, the sera containing the antibodies having been produced by ingenious animal experiments. Then followed another latent period, which ended with the discovery of the Rhesus system in 1940. It is true that the original discovery of Rhesus was also due to animal experiments, but it was immediately found that the same antigen, or something closely similar, was responsible for the great bulk of haemolytic disease of the foetus and newborn and also for the great bulk of transfusion reactions up to that time (when ABO groupings were compatible). The modern phase of the science of serology had begun. The systems subsequently established, together with new antigens belonging to the older systems, have been discovered by the detection of new antigen-antibody reactions in cases of haemolytic disease and in cases of unexpected transfusion incompatibility. Some of the antigens have proved to be very weak stimulators of antibody formation and prolonged observation may be necessary before the opportunity arises, but judging by the progress of the past 12 years it is likely that there are other, perhaps many other, antigens on the red cells that sooner or later will be discovered when ultimately they do produce an antibody.

The first point, and a very important one, underlying the genetic simplicity of the blood groups is that the presence of each antigen is determined by a corresponding gene. It is a complete one-to-one correspondence; there are no environmental reactions. It may be that this direct relationship means that there are relatively few developmental steps between the gene in the chromosome and the antigen on the surface of the erythrocytes. The second point making for simplicity is that as a general rule there is no dominance. For example, M and N depend on a pair of alternative genes. A person with two M genes has red cells which react with anti-M but not with anti-N, a person with two N genes has reds which react with anti-N but not with anti-M, a person with one M gene and one N gene has reds which react with both antisera. M is not dominant to N nor is N to M, and so, given the two antisera, the genetic constitution of any individual can be completely specified.

The genetic simplicity of the blood groups means that only the barest elements of chromosome behaviour need be recalled in order to understand their genetics. We need not even consider the sex chromosomes, for so far no sex-linked blood group system has come to light. These essentials are recalled in Fig. 1.

The chromosomes are paired and so the genes they bear are also paired. Prior to a somatic division the 24 pairs of chromosomes have doubled, so the two daughter cells contain the very same chromosomes and genes as were present in the mother cell. Prior to the formation of the

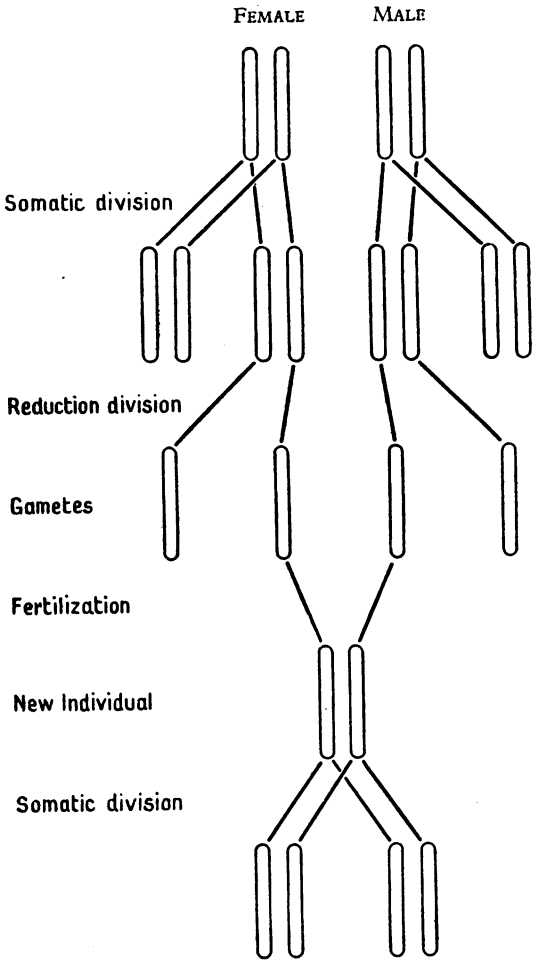
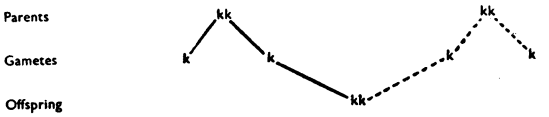


FIG. 1.—Behaviour of a chromosome pair in somatic division, the reduction division and fertilization.

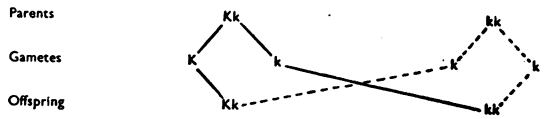
gametes, however, a special division, the reduction division, takes place, the result being that the chromosome pairs separate bodily; hence an ovum or spermatozoon contains 24 single chromosomes. At fertilization the 24 pairs are reconstituted, one chromosome of each pair being contributed by the father and one by the mother. In the diagrams which follow the letters stand for the genes and also, owing to the one-to-one correspondence already stressed, they can equally stand for the antigens. Moreover, as it has not yet been proved that any two blood group systems depend on genes situated on the same chromosome pair, the letters can also stand for the chromosomes bearing the genes.

As an example of a so-far simple system we may take Kell. In 1946 Coombs, Mourant and Race discovered a new antibody in the serum of a woman who had a child suffering from haemolytic disease. This antibody reacted with the red cells of her husband and of her two children and with about 10 per cent. of random bloods. The gene corresponding to the antigen, symbolized by K, was found to be dominant, that is, K-positive individuals can be of two kinds for they may have two K genes or else one K gene and one k gene, which at this stage of the story was the hypothetical alternative gene. K-negative individuals must have two k genes. It was estimated that the proportion of K genes in our population is 5 per cent. and of k genes 95 per cent. Hence about 90 per cent. of individuals are K-negative and about 10 per cent. K-positive. As K is so much rarer than k, nearly all the 10 per cent. have one gene of each kind; only about 0.25 per cent. of people have two K genes.

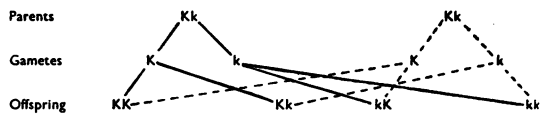
Diagrams based on Fig. 1 at once show what happens in the various possible matings. If both parents are K-negative all offspring are also K-negative.



If one parent is K-positive, with the usual constitution Kk, and the other K-negative, the result is, on the average, K-positive and K-negative children in equal proportions.



Should both parents be K-positive, with one gene of each kind, the result is:



On the average there are three K-positives and one K-negative in every four. One of the three, however, has two K genes, the other two only one, but with only one antiserum available they cannot be distinguished serologically.

It may be stressed here that diagrams of these three types cover all the possibilities in all the blood group systems. If both parents have genes

of one kind there is only one kind of offspring. If one parent has unlike genes and the other like there are two kinds of offspring in equal proportions. If both parents have unlike genes there are three kinds of offspring (or possibly four, as will be mentioned later).

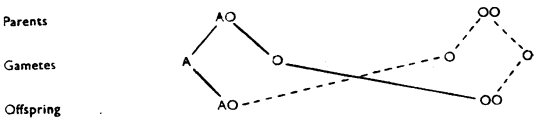
It is easy to see what the result will be for other possible matings. KK × KK gives KK only, KK × Kk gives KK and Kk in equal proportions, KK × kk gives Kk only.

The apparent dominance and recessiveness, however, only lasted for three years. In 1949 Levine and his co-workers discovered an antibody in the serum of the mother of a child who suffered from mild haemolytic disease; this proved to be anti-k. The new antiserum reacted with all but one in 400 bloods, for as we have just seen that is the frequency in the population of persons who have two K genes. The diagrams are, of course, unchanged, but with the new discovery it became possible to distinguish KK from Kk. KK blood reacts with anti-K but not with anti-k; kk blood reacts with anti-k but not with anti-K; Kk blood reacts with both antisera.

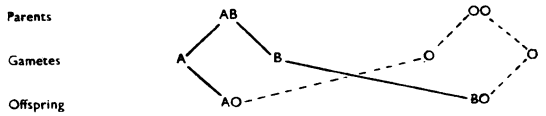
It will be seen, therefore, that in blood group genetics dominance and its reciprocal, recessiveness, are rather formal and provisional conceptions. K was dominant to k only until anti-k was discovered. Had anti-k been discovered first k would have been considered dominant. Now one cannot say either that K is dominant to k or k to K. Each alternative gene produces an effect which is undisturbed by the presence of the other. This has been the usual history of the blood group systems and perhaps ultimately it will prove true of all of them.

Only two extensions of the foregoing simple scheme are needed in order to follow the apparent complexities of some of the other blood group systems. The first extension is illustrated by the ABO system. Instead of a pair of genes there may be more than two which are alternative to each other; in this instance there are three, namely A, B and O. A given individual has two of these genes, either the same or different. A person of group O has two O genes; of group A either two A genes or one A and one O; of group B either two B genes or one B and one O; of group AB one A gene and one B gene. Thus in the rather formal sense previously mentioned A and B are both dominant to O, whereas between A and B there is no dominance or recessiveness. O is not merely the absence of A or B however. There is an O antigen, though up to the present no usable anti-O serum is available which would enable persons of constitution AA to be distinguished from those of constitution AO, or those of BB from BO.

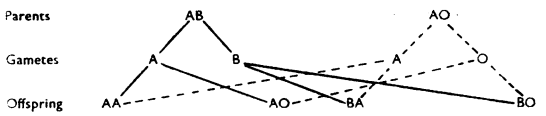
It is easy, given the plan of Fig. 1, to deduce the results of any mating. Any result can be accommodated by one of the three diagrams used for the Kell system. For example:



The mating AB × O gives a peculiar result:



The consequence is that no children can be of the same blood group as either parent. Or, to illustrate the point that offspring of four different genetic constitutions may result from a mating (the maximum degree of complexity with any blood group):



There are further subdivisions of A: A_1 and A_2, both of which are common, and also A_3 and A_4, which are rare. The distinctions depend on strength of reaction, but are absolute. This merely extends the scheme. In the sense formerly used, A_1 is dominant to A_2, A_3 and A_4; A_2 to A_3 and A_4; A_3 to A_4. The alternative genes are A_1, A_2, A_3, A_4, B, O. A given individual has two of these genes, either the same or different, and the results of any mating can be worked out equally easily.

A second extension of the basic scheme is needed in order to follow the genetics of Rhesus, which at first sight may seem complicated. Instead of a single gene on a particular chromosome, we now have to think of three genes situated very close together, so close that they have not been observed to separate by the process of crossing-over. At one point, or locus, we have C or c, at the second D or d, at the third E or e. All the corresponding antigens have produced antibodies, though d is such a weak stimulator that no usable antiserum has ever been available; indeed its occurrence is not accepted by some workers.

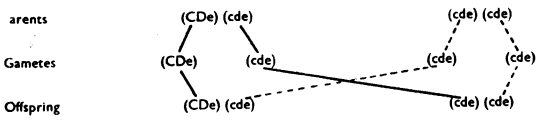
It should be mentioned in passing that D is much the most important antigen, being responsible for far more transfusion reactions and haemolytic disease than all the others put together. So it is

that we can still talk of Rh-negatives and Rh-positives. Rh-positives are persons who possess D, while Rh-negatives do not. If we think of this one antigen only the genetics follow the simple plan given above for K during the short time before anti-k was discovered.

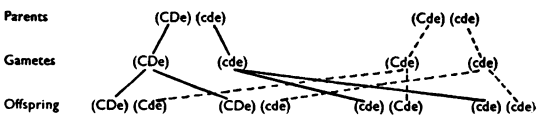
Reverting to the fuller scheme the single letters stand for genes which determine the corresponding antigens, which in turn can be recognized by the various single antisera. These are the serological units, but they are not the genetic units that are transmitted from parent to child. The genetic unit is a block of three closely linked genes, for example (CDe) or (cde). There are eight possible combinations. The frequencies with which the eight combinations occur are very different. In our population they are approximately:

	Per cent.
(CDe)	42
(cde)	39
(cDE)	14
(cDe)	2½
(cdE)	1¼
(Cde)	1
(CDE)	¼
(CdE)	Very rare

Any given individual has two of these compound genes, either the same or different. The results of any mating can be worked out just as easily as in the uncomplicated instances considered previously; only the same three standard diagrams are needed. Thus, for example, let us take the commonest mating of Rhesus positive and Rhesus negative individuals:



No mating can yield more than four kinds of offspring. For example:



Just as before, if both parents have compound genes of the same kind all the offspring are of the same constitution. If one parent has genes of different kinds there are two kinds of offspring; if both parents have genes of different kinds there are three or four kinds of offspring. And that is all.

The final step is to put both extensions together. In addition to the usual six (simple) genes of the Rhesus system, other rare alternatives may occur, for example in addition to C and c, there are the rarer alternatives C^w, c^v and C^u. This extends the scheme but the principles are the same, namely a chromosome containing a block of three, one each from the C, D and E loci, with each individual person bearing two of the compound genes, either the same or different.

It should be added, however, that very recently a fourth pair of elementary genes has been found, closely linked to the previous three. These are called F and f. The permutations and combinations are undoubtedly becoming very numerous but the genetic principles remain the same and are equally easy to understand though, of course, no one will underestimate the refinements and complexities of the truly remarkable serological advances that have been made in so short a space of time.

The theory of closely linked loci now applies to an extension of the MN system which has been established in recent years. Two new genes determining two new antigens have been discovered. They are called S and s. As in the Rhesus system, very close linkage apparently exists so that what are transmitted as genetic units are the compound genes (MS), (Ms), (NS) and (Ns).

A striking demonstration of the essential simplicity of the genetics of the human blood groups is provided by the speed with which the genetics are established after each new serological advance. A new blood group system is discovered, or a new antigen belonging to an old one, and then in a remarkably short space of time and with observations on a number of families which can only strike those familiar with other and more complicated aspects of human genetics as absurdly few, the genetics of the new system, or antigen, are firmly established. Thus it is that provided a very few principles are grasped and applied, the genetics of the blood groups can be followed quite easily by those who are not serologists and who, indeed, may have no more than a limited acquaintance with the science of genetics.

It is impossible within the compass of a short paper to do more than illustrate the principles underlying the inheritance of the blood groups. Those who wish to pursue the subject, or who are interested in the genetics of a particular system or systems, will find a clear and most readable account in Race and Sanger's ' Blood Groups in Man,' Blackwell Scientific Publications, 1950.